NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREFOR

RELATED PATENT APPLICATIONS

This application is a Continuation-In-Part of ~~currently pending~~ abandoned U.S. Pat. App. No. 08/124,392, filed 9/20/93

TECHNICAL FIELD

This invention generally relates to compositions of nicotinic acid useful for treating hyperlipidemia and methods of treating hyperlipidemia employing such compositions. More particularly, the present invention employs a composition of nicotinic acid, derivatives and mixtures thereof, and a swelling agent to form a time release sustaining composition for nocturnal or evening dosing. Specifically, the present invention employs a composition of nicotinic acid and hydroxypropyl methylcellulose to treat hyperlipidemia in a once per day oral dosage form given during the evening hours.

BACKGROUND OF THE INVENTION

Nicotinic acid has been used for many years in the treatment of hyperlipidemia. This compound has long been known to exhibit the beneficial effects of reducing total cholesterol, low density lipoproteins or "LDL cholesterol", triglycerides and apolipoprotein a (Lp(a)) in the human body, while increasing desirable high density lipoproteins or "HDL cholesterol".

Nicotinic acid has normally been administered three times per day after meals. This dosing regimen is known to provide a very beneficial effect on blood lipids as discussed in Knopp et al; "Contrasting Effects of Unmodified and Time-Release Forms of Niacin on Lipoproteins in Hyperlipidemic Subjects: Clues to Mechanism of Action of Niacin"; Metabolism 34/7, 1985, page 647. The chief advantage of this profile is the ability of nicotinic acid to decrease total cholesterol, LDL cholesterol, triglycerides and Lp (a) while increasing HDL particles. While such a regimen does produce beneficial effects, cutaneous flushing and the like still often occurs in the hyperlipidemics to whom the compound is administered.

In order to avoid or reduce the cutaneous flushing a number of materials have been suggested for administration with an effective antihyperlipidemic amount of nicotinic acid, including guar gum in U.S. Pat. No. 4,965,252, and mineral salts as disclosed in U.S. Pat. No. 5,023,245; or inorganic magnesium salts as reported in U.S. Pat. No. 4,911,917. These materials have been shown to the cutaneous flushing of the side effects commonly associated with nicotinic acid treatment.

Another method of avoiding or reducing the side effects associated with immediate release niacin is the use of sustained release formulations. Sustained release formulations are designed to slowly release the compound from the tablet or capsule. The slow drug release reduces and prolongs blood levels of drug and thus minimizes the side effects. Sustained release formulations of niacin have been developed, such as Nicobid™ capsules (Rhone-Poulenc Rorer), Endur-acin™ (Innovite Corporation) and Pat. No. 5,126,145 which describes a sustained release niacin formulation containing two different types of hydroxypropyl methylcellulose and a hydrophobic component.

Studies in hyperlipidemic patients have been conducted with a number of sustained release niacin products. These studies have demonstrated that the sustained release products do not have the same advantageous lipid altering effects as immediate release niacin, and in fact often have a worse side effect profile compared to the immediate release product. The major disadvantage of the sustained release formulations, as can be seen in Knopp et al., 1985, is the significantly lower reduction in triglycerides (-2% for the sustained release versus -38% for the immediate release) and lower increase in HDL cholesterol, represented as HDL_2 particles which are known by the art to be most beneficial, (-5% for the sustained release versus +37% for the immediate release).

Additionally, sustained release niacin formulations have been noted as causing greater incidences of liver toxicity as described in Henken et al (Am J Med 91:1991 1991) and Dalton et al (Am J Med 93: 102 1992). There is also great concern regarding the potential of these formulations in disrupting glucose metabolism and uric acid levels.

In a recent edition of the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA), an article appeared which presented research results investigating the liver toxicity problems associated with a sustained release form of nicotinic acid. "A Comparison of the Efficacy and Toxic Effects of Sustained- vs Immediate-Release Niacin in Hypercholesterolemic Patients", McKenney et al., JAMA, Vol. 271, No. 9, March 2, 1994, page 672. The article presented a study of twenty-three patients. Of that number 18 or 78 percent were forced to withdraw because liver function tests (LFTs) increased indicating potential liver damage. The conclusion of the authors of that article was that the sustained release form of niacin "should be restricted from use."

A similar conclusion was reached in an article authored by representatives of the Food and Drug Administration and entitled "Hepatic Toxicity of Unmodified and Time-Release Preparations of Niacin", Rader, et al., THE AMERICAN JOURNAL OF MEDICINE, Vol. 92, January 1992, page 77. Because of these

3

studies and similar conclusions drawn by other heath care professionals, the sustained release forms of niacin have experienced limited utilization.

Therefore, it can be seen from the scientific literature that there is a need for development of a sustained release niacin formulation and a method of delivering said formulation which would provide hyperlipidemic patients with "balanced lipid alteration", i.e. reductions in total cholesterol, LDL cholesterol, triglycerides and Lp(a) as well as increases in HDL cholesterol with an acceptable safety profile, especially as regards liver toxicity and effects on glucose metabolism and uric acid levels.

SUMMARY OF THE INVENTION

It is therefore, an object of the present invention to provide a composition of nicotinic acid or any compound which is metabolized by the body to form nicotinic acid for treating hyperlipidemia.

It is another object of the present invention to provide a composition as above, which has a time release sustaining characteristic.

It is yet another object of the present invention to provide a method for employing a composition as above, for treating hyperlipidemia, which results in little or no liver damage.

At least one or more of the foregoing objects, together with the advantages thereof over the known art relating to the treatment of hyperlipidemia, which shall become apparent from the specification which follows, are accomplished by the invention as hereinafter described and claimed.

In general the present invention provides an improved antihyperlipidemia composition of the oral type employing an effective antihyperlipidemic amount of nicotinic acid, wherein the improvement comprises compounding the nicotinic acid with from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose per hundred parts by weight of tablet or formulation.

The present invention also provides an orally administered antihyperlipidemia composition which comprises from about 30% to about 90% parts by weight of nicotinic acid; and, from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose.

The present invention also includes a method of treating hyperlipidemia in a hyperlipidemic. The method comprises the steps of forming a composition which comprises an effective antihyperlipidemic amount of nicotinic acid and an amount of excipients to provide sustained release of drug. The method also includes the step of orally administering the composition to the hyperlipidemic nocturnally.

A method of treating hyperlipidemia in a hyperlipidemic according to the invention, comprises dosing the hyperlipidemic with an effective antihyperlipidemic amount of nicotinic acid or compound metabolized to nicotinic acid by the body. The dose is given once per day in the evening or at night, combined with a pharmaceutically acceptable carrier to produce a significant reduction in total and LDL cholesterol as well as a significant reduction in triglycerides and Lp(a), with a significant increase in HDL cholesterol.

PREFERRED EMBODIMENTS FOR CARRYING OUT THE INVENTION

The present invention employs nicotinic acid or a compound other than nicotinic acid itself which the body metabolizes into nicotinic acid, thus producing the same effect as described herein. The other compounds specifically include, but are not limited to the following: nicotinyl alcohol tartrate, d-glucitol hexanicotinate, aluminum nicotinate, niceritrol and d,l-alpha-tocopheryl nicotinate. Each such compound will be collectively referred to hereinbelow by "nicotinic acid."

As stated hereinabove, nicotinic acid has been employed in the past for the treatment of hyperlipidemia, which condition is characterized by the presence of excess fats such as cholesterol and triglycerides, in the blood stream. According to the present invention, a sustained release composition of nicotinic acid is prepared as an example. By "sustained release" it is understood to mean a composition which when orally administered to a patient to be treated, the active ingredient will be released for absorption into the blood stream over a period of time. For example, it is preferred that in a dosage of about 1500 milligrams (hereinafter "mgs") of nicotinic acid, approximately 100 percent of the nicotinic acid will be released to the blood stream in about 4 to about 24 hours.

The specific sustained release composition according to the present invention employs an effective antihyperlipidemic amount of nicotinic acid. By "effective antihyperlipidemic amount" it is understood to mean an amount which when orally administered to a patient to be treated, will have a beneficial effect upon the physiology of the patient, to include at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream. An exemplary effective antihyperlipidemic amount of nicotinic acid would be from about 250 mgs to about 3000 mgs of nicotinic acid to be administered according to the invention as will be more fully described hereinbelow. This amount will vary dependent upon a number of variables, including the physiological needs of the patient to be treated.

5

Preferably, there is also included in the sustained release composition according to the present invention, a swelling agent which is compounded with the nicotinic acid, such that when the composition is orally administered to the patient, the swelling agent will swell over time in the patient's gastrointestinal tract, and release the active nicotinic acid, or a compound which produces nicotinic acid into the gastrointestinal system for absorption into the blood stream, over a period of time. As is known in the art, such swelling agents and amounts thereof, may be preselected in order to control the time release of the active ingredient. Such swelling agents include, but are not limited to, polymers such as sodium carboxymethylcellulose and ethylcellulose and waxes such as bees wax and natural materials such as gums and gelatins or mixtures of any of the above. Because the amount of the swelling agent will vary depending upon the nature of the agent, the time release needs of the patient and the like, it is preferred to employ amounts of the agent which will accomplish the objects of the invention.

An exemplary and preferred swelling agent is hydroxypropyl methylcellulose, in an amount ranging from about 5% to about 50% parts by weight per 100 parts by weight of tablet or formulation. The preferred example will ensure a sustained time release over a period of approximately 4-24 hours as demonstrated by in vitro dissolution techniques known to the art.

A binder may also be employed in the present compositions. While any known binding material is useful in the present invention, it is preferred to employ a material such as one or more of a group of polymers having the repeating unit of 1-ethenyl-2-pyrrolidinone. These polymers generally have molecular weights of between about 10,000 and 700,000, and are also known as "povidone".

Amounts of the binder material will of course, vary depending upon the nature of the binder and the amount of other ingredients of the composition. An exemplary amount of povidone in the present compositions would be from about 1% to about 5% by weight of povidone per 100 parts by weight of the total formulation.

Processing aids such as lubricants, including stearic acid, may also be employed, as is known in the art. An exemplary amount of stearic acid in the present compositions would be from about 0.5% to about 2.0% by weight per 100 parts by weight of tablet or formulation.

General Experimental

In order to demonstrate the effectiveness of the compositions and method of the present invention over known antihyperlipidemia compositions and methods heretofore known in the art, a number of substantially identical

6

composition were prepared according to the disclosure hereinabove. The composition ingredients and amounts are listed in TABLE I hereinbelow.

T70X

TABLE I
Test Tablet Composition

Ingredient	375 mg	500 mg	750 mg
Nicotinic Acid	375.0	500.0	750.0
Hyroxypropyl methylcellulose	188.7	203.0	204.7
Povidone	12.9	17.2	25.9
Stearic Acid	5.8	7.3	9.9
TOTAL	582.4 mg	727.5 mg	990.5 mg

The ingredients were compounded together to form a tablet. Two study groups consisting of eleven and fourteen patients each were formed. Blood samples were taken from the patients, and tested for total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol to establish baseline levels from which fluctuations in these lipids could be compared. The patients were then placed upon a regimen of the above discussed tablets, totaling approximately 1500 mg of nicotinic acid, once per day before going to bed. After eight weeks of this regimen, the patients were again tested for lipid profiles. The results of the tests conducted at eight weeks, showing the changes in the lipid profiles as a percentage change from the baseline, are reported in the table hereinbelow. Positive numbers reflect percentage increases and negative numbers reflect percentage decreases in this table.

7

T80X

TABLE II
Patient Study Lipid Profile Data

Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL2-C	Lp(a)
GROUP A							
1	-8.2	-12.0	NA	-17.3	22.0	NA	NA
2	-5.9	-27.0	NA	-28.7	65.0	NA	NA
3	-15.1	-13.0	NA	-22.0	-9.1	NA	NA
4	-3.3	-10.0	NA	61.6	3.8	NA	NA
5	-16.5	-17.7	NA	-28.8	11.1	NA	NA
6	-12.4	-25.9	NA	-42.0	51.6	NA	NA
7	-24.2	-31.4	NA	-39.4	12.5	NA	NA
8	-6.7	-7.4	NA	-42.4	18.8	NA	NA
9	4.5	1.1	NA	7.2	9.2	NA	NA
10	2.8	-0.2	NA	-2.7	22.9	NA	NA
11	-13.0	-9.4	NA	-54.0	44.3	NA	NA
Mean	-8.9	-13.9	NA	-18.9	23.0	NA	NA
p-Value	0.0004	0.0001		0.0371	0.0068		
GROUP B							
1	-19.2	-27.1	-24.4	-33.4	20.0	22.3	-81.9
2	-32.2	-35.7	-28.0	-60.4	4.3	3.2	-25.3
3	-21.4	-33.6	-35.6	-33.4	30.4	38.6	-17.4
4	-19.9	-24.6	-15.1	-20.8	9.6	16.1	-27.0
5	-3.3	-2.1	-29.4	-41.1	5.8	2.4	-22.4
6	PATIENT WITHDREW FROM STUDY						
7	23.1	-32.6	-42.6	-58.6	49.2	68.9	-14.3
8	24.8	34.0	-28.4	5.5	6.5	-6.8	NA
9	10.1	12.0	-16.8	-11.6	20.7	-12.3	40.6
10	-2.9	-7.7	-28.0	-59.0	53.1	70.5	-41.2

8

TABLE II Continued

Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL^2-C	Lp(a)
GROUP B							
11	-10.5	-18.8	-25.3	-53.4	31.8	39.7	NA
12	-20.0	-30.8	-30.4	11.7	21.1	25.0	-28.4
13	17.4	16.8	-17.5	-17.5	51.3	51.9	38.5
14	-9.4	-16.6	-32.0	-46.9	52.3	67.6	17.6
Mean	-8.7	-12.8	-32.2	-27.2	25.3	30.1	-17.9
p-Value	0.0002	<0.0001	0.0001	<0.001	<0.0001	0.0002	<0.0188
Combined	-8.7	-13.3	Gp B	-26.1	25.3	Gp B	Gp B
p-Value	0.0002	<0.0001	only	<.0001	<0.0001	only	only

The data reported in TABLE II shows that the LDL levels in the Group A patients had a mean decrease of -13.9% and triglyceride decrease of -18.9%. HDL cholesterol levels, the beneficial cholesterol, were raised by 23.0% in this Group. Similar results were obtained with the Group B patients. These studies demonstrate that dosing the sustained release formulation during the evening hours or at night provides reductions in LDL cholesterol levels equal to immediate release niacin on a milligram per milligram basis, but superior reductions in triglyceride reductions when compared to sustained release formulations dosed during daytime hours on a milligram per milligram basis. Additionally, the increases in HDL cholesterol obtained from dosing the sustained release formulation during the evening or at night were +23.0% for one group and +25.3% for the other group. Dosing during the evening therefore provides reduction in LDL cholesterol plus significant decreases in triglycerides and increases in HDL cholesterol with once-a-day dosing.

Groups A and B were also tested for liver enzymes (AST, ALT and Alkaline Phosphatase), uric acid and fasting glucose levels at the start of the study described hereinabove (to form a baseline) and at two, four and eight week intervals. The results of these tests are listed in TABLES III-VII hereinbelow.

T160X

TABLE III

THE EFFECT OF NIASPAN™ THERAPY ON AST (SGOT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

		Weeks Of Therapy With NIASPAN™			
Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	28	29	25	24	0-50
2	24	25	24	26	0-50
3	17	18	22	21	0-50
4	14	16	15	17	0-50
5	22	NA	32	52	0-50
6	21	17	17	14	0-50
7	17	17	14	18	0-50
8	20	21	22	22	0-50
9	16	16	17	20	0-50
10	18	21	21	25	0-50
11	21	21	22	21	0-50
GROUP B					
1	23	25	38	33	0-50
2	20	20	21	21	0-50
3	15	20	18	19	0-50
4	25	22	25	26	0-50
5	23	21	17	18	0-50
6	PATIENT WITHDREW DUE TO FLUSHING				
7	21	18	18	19	0-50
8	18	19	18	19	0-50
9	15	16	18	15	0-50
10	16	15	19	28	0-50
11	20	22	24	28	0-50
12	23	25	28	22	0-50
13	20	15	20	19	0-50

10

TABLE III Continued

Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP B					
14	18	25	20	18	0-50
Combined Mean	19.8	20.4	20.8	21.1	
Change From Baseline		+3.0%	+5.1%	+6.6%	

Level of Significance: p=0.4141

T120X

TABLE IV

THE EFFECT OF NIASPAN™ THERAPY ON ALT (SGPT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

		Weeks Of Therapy With NIASPAN™			
Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	32	28	39	30	0-55
2	24	25	23	26	0-55
3	18	23	30	30	0-55
4	7	13	14	14	0-55
5	14	NA	43	46	0-55
6	22	11	14	10	0-55
7	9	7	11	7	0-55
8	16	18	23	21	0-55
9	14	17	20	14	0-55
10	14	15	17	19	0-55
11	18	18	20	16	0-55
GROUP B					
1	16	17	27	29	0-55
2	16	14	15	22	0-55
3	13	21	13	16	0-55
4	23	20	26	17	0-55
5	21	23	17	15	0-55
6	PATIENT WITHDREW DUE TO FLUSHING				
7	21	16	18	21	0-55
8	18	20	17	18	0-55
9	11	5	11	8	0-55
10	8	10	14	17	0-55
11	17	12	18	16	0-55
12	14	18	20	16	0-55
13	14	NA	11	10	0-55

12

TABLE IV Continued

Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP B					
14	23	23	19	19	0-55
Combined Mean	17.7	17.5	19.3	18.2	
Change From Baseline		-1.1%	9.0%	+2.8%	

Level of Significance: p=0.3424

T140X

TABLE V
THE EFFECT OF NIASPAN™ THERAPY ON ALKALINE PHOSPHATASE LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

	Weeks Of Therapy With NIASPAN™				
Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	52	56	57	55	20-140
2	103	100	89	102	20-140
3	54	45	53	51	20-140
4	70	68	71	91	20-140
5	77	NA	74	81	20-140
6	55	48	49	51	20-140
7	72	71	79	75	20-140
8	55	49	47	50	20-140
9	53	55	56	45	20-140
10	74	73	75	75	20-140
11	18	18	20	16	20-140
GROUP B					
1	73	67	89	95	20-140
2	82	64	72	71	20-140
3	73	69	72	82	20-140
4	37	36	37	38	20-140
5	65	53	54	61	20-140
6	PATIENT WITHDREW DUE TO FLUSHING				
7	64	58	58	58	20-140
8	79	78	65	73	20-140
9	94	92	103	93	20-140
10	69	67	70	65	20-140
11	59	67	63	72	20-140
12	65	59	59	63	20-140
13	64	68	66	64	20-140

TABLE V Continued

Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP B					
14	72	61	59	64	20-140
Combined Mean	65.5	61.5	63.3	65.8	
Change From Baseline		-6.1%	-3.4%	+0.005%	

Level of Significance: p=0.0236

T150X

TABLE VI
THE EFFECT OF NIASPAN™ THERAPY ON URIC ACID LEVELS (mg/dL)
(1500 mgs dosed once-a-day at night)
(n = 28)

		Weeks Of Therapy With NIASPAN™				
	Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
	GROUP A					
10	1	5.2	5.0	4.8	4.3	4.0-8.5
	2	4.0	4.6	4.5	6.2	2.5-7.5
	3	6.3	7.0	6.5	6.2	4.0-8.5
	4	3.1	4.6	4.2	3.8	2.5-7.5
	5	3.4	NA	3.3	4.2	2.5-7.5
15	6	6.6	5.5	5.6	4.7	4.0-8.5
	7	3.8	4.5	4.3	4.9	2.5-7.5
	8	4.4	3.8	5.1	4.5	2.5-7.5
	9	3.9	4.5	4.6	3.5	2.5-7.5
	10	2.6	2.9	2.8	2.7	2.5-7.5
20	11	4.7	5.5	5.2	5.3	2.5-7.5
	GROUP B					
	1	3.7	4.2	4.7	3.5	2.5-7.5
	2	2.8	3.5	3.6	2.3	4.0-8.5
25	3	4.2	5.3	5.5	5.3	2.5-7.5
	4	4.7	3.9	5.1	3.6	4.0-8.5

	5	3.7	4.1	4.1	3.8	2.5-7.5
	6		PATIENT WITHDREW DUE TO FLUSHING			
	7	5.8	6.6	6.6	6.8	2.5-7.5
	8	4.7	4.3	5.4	5.6	2.5-7.5
5	9	3.7	4.6	5.1	3.8	2.5-7.5
	10	4.2	5.0	4.4	8.5	2.5-7.5
	11	1.9	3.0	2.8	5.0	2.5-7.5
	12	5.6	5.4	6.2	5.6	4.0-8.5
	13	4.2	4.6	4.6	5.3	2.5-7.5
10	**GROUP B**					
	14	5.5	5.4	6.1	5.3	2.5-7.5
	Combined Mean	4.54	4.82	4.92	4.86	*p=0.3450
15	Change From Baseline		+6.2%	+8.4%	+7.0%	

*Level of Significance: p=0.3450

TABLE VII
THE EFFECT OF NIASPAN™ THERAPY ON FASTING GLUCOSE LEVELS (mg/dL)
(1500 mgs dosed once-a-day at night)
(n = 28)

		Weeks Of Therapy With NIASPAN™				
	Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
	GROUP A					
	1	114	122	123	110	70-115
	2	101	105	107	101	80-125
	3	99	98	109	103	70-115
	4	100	118	94	94	80-125
	5	89	NA	82	103	80-125
	6	97	103	94	107	70-115
	7	85	107	100	94	80-125
	8	98	107	103	101	80-125
	9	97	97	100	110	80-125
	10	94	101	111	97	70-115
	11	102	103	95	95	80-125
	GROUP B					
	1	101	97	83	99	70-115
	2	90	95	96	89	80-125
	3	96	98	95	97	70-115
	4	116	139	113	125	80-125
	5	88	92	91	95	70-115
	6	PATIENT WITHDREW DUE TO FLUSHING				
	7	106	114	118	117	70-115
	8	95	106	106	108	70-115
	9	81	92	84	92	70-115
	10	108	117	122	105	70-115
	11	85	106	106	108	70-115
	12	92	89	101	86	80-125

TABLE VII Continued

Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP B					
13	99	105	94	100	70-125
14	100	108	84	107	70-125
Combined Mean	98.4	105.8	101.6	102.3	
Change From Baseline		+7.5%	+3.3%	+4.0%	

Level of Significance: p=0.0021

In order to provide a comparison between the state of the art prior to the present invention, and in order to quantify the magnitude of the improvement that the invention provides over the prior art, another study was conducted. This study included 240 patients dosed according to the present invention as described hereinabove. Compared to this group was the group of patients studied by McKenney et al., as reported hereinabove. The results of this study are reported in TABLE VIII hereinbelow.

TABLE VIII
A Comparison of Changes in Liver Function Tests

	DOSE							
	0	**500**	**1000**	**1500**	**2000**	**2500**	**3000**	**TOTAL**
McKenney SR[b] Niacin[a]								
AST	23.8	27.9	40.4	36.6	56.5	na	97.0	
%	--	117	170	154	237	na	408	
Invention Dosage[c]								
AST	24.3	na	23.7	27.5	26.6	27.6	27.8	
%	--	na	98	113	109	114	114	
McKenney SR Niacin								
ALT	25.6	29.5	36.3	39.0	59.1	na	100.0	
%	--	115	142	152	231	na	391	
Invention Dosage								
ALT	21.4	na	18.7	22.6	21.3	22.4	21.8	
%	--	na	87	106	100	105	102	
McKenney SR Niacin								
ALK	95	95	106	105	136	na	135	
%	--	100	112	111	143	na	142	

TABLE VIII (continued)

	DOSE							
	0	500	1000	1500	2000	2500	3000	TOTAL
Invention Dosage								
ALK	74.7	na	73.9	76.1	73.4	76.7	78.0	
%	--	na	99	102	98	103	104	
McKenney SR Niacin								
Drop	--	0	2	2	7	na	7	18
n	--	--	--	--	--	--	--	23
%	--	0	9	9	30	na	30	78
Invention Dosage								
Drop	--	--	0	0	0	0	0	0
n	--	--	26	67	97	35	15	240
%	--	--	0	0	0	0	0	0
1 year	--	--	15	46	77	31	15	184
1 year	--	--	58	69	79	89	100	77

[a] Dosed twice-per-day as described in "A Comparison of the Efficacy and Toxic Effects of Sustained - vs Immediate - Release Niacin in Hypercholesterolemic Patients" by McKenney et al. Journal of the American Medical Association, March 2, 1994; Vol. 271, No. 9, pages 672-677.

[b] SR is "sustained release"

[c] Dosed once-per-day at night

The results of the comparison of the studies reported in TABLE VIII show that the control group (the McKenney group) had 18 of 23, or 78 percent of the patients therein drop out of the test because of an increase in their respective liver function tests. The patients withdrew at the direction of the investigator. In comparison, a group of 240 patients treated according to the present invention had zero patients drop out, based upon the same criteria for withdrawal. The tests results reported above indicate that this sustained release dosage form caused no elevation in liver function tests (i.e., no liver damage), no elevations in uric acid and only a small, 7.5% increase in fasting glucose levels which in fact decreased during continued therapy.

Thus it should be evident that the compositions and method of the present invention are highly effective in controlling hyperlipidemia in hyperlipidemics, by reducing the levels of LDL cholesterol, triglyceride and Lp(a) while increasing HDL cholesterol levels. The present invention is also demonstrated not to cause elevations in liver function tests, uric acid or glucose levels for the hyperlipidemics.

Based upon the foregoing disclosure, it should now be apparent that the use of the compositions and methods described herein will carry out the objects set forth hereinabove. It is, therefore, to be understood that any variations in sustained release formulation evident fall within the scope of the claimed invention and thus, the selection of specific component elements can be determined without departing from the spirit of the invention herein disclosed and described. In particular, sustained release excipients, binders and processing aids according to the present invention are not necessarily limited to those exemplified hereinabove. Thus, the scope of the invention shall include all modifications and variations that my fall within the scope of the attached claims.